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Orbital Rhabdomyosarcomas and Related Tumors in Childhood: Relationship of Morphology to Prognosis—An Intergroup Rhabdomyosarcoma Study

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Children and adolescents who develop rhabdomyosarcoma (RMS) and related sarcomas in the orbit and treated on Intergroup Rhabdomyosarcoma protocols have had an extremely high cure rate. This study evaluates the possible relationship between their tumor morphologic subtypes and this high cure rate. The histology of tumors was re-reviewed from 229 of the 264 patients with tumors of the orbit, conjunctiva, and eyelids treated on Intergroup Rhabdomyosarcoma Studies (IRS) I, II, III, and IV pilot protocols, and followed through July, 1992. Immunohistochemistry was applied in selected cases. Clinical correlations were done on all 264 cases including both the re-reviewed cases and those reviewed only by the IRS Pathology committee. The 5-year survival rate of 24 children with alveolar RMS was 74% ($p < .001$). All five infants diagnosed to have an alveolar RMS died before the age of one. Two hundred and twenty-one patients (84%) had embryonal RMS. About three-fourths of the re-reviewed embryonal RMS tumors showed only minimal rhabdomyoblastic differentiation. Thirty-one had a spindle cell RMS, two were anaplastic variants. The 5-year survival rate for patients with embryonal RMS subtypes combined was 94%, and 97% for the 144 patients with poorly differentiated embryonal RMS. In contrast, 190 of 432 IRS II patients treated for poorly differentiated embryonal RMS located in extraocular sites had a 66% survival estimate. Med. Pediatr. Oncol. 29:51–60, 1997.

Key words: rhabdomyosarcoma; orbit; childhood; prognosis; morphology; alveolar; infants

INTRODUCTION

Orbital rhabdomyosarcomas (RMS) and related sarcomas of children and adolescents represent a unique group of sarcomas. When treated by surgery alone the tumor displays a highly malignant potential by developing recurrences and metastases. Four major studies performed before multidisciplinary treatment was introduced showed that only 30% of patients were alive 3 years after the tumor was diagnosed [1]. Exenteration was the most frequent and in many instances the only operative procedure. The addition of radiation therapy and chemotherapy has dramatically changed the outcome of patients with orbital RMS [2–7]. The 3-year tumor-free survival rate for 127 localized orbital RMS patients enrolled on the IRS I and II has been estimated to be 93% [4] despite reduction of surgery to subtotal tumor resection or biopsy only [3,8]. A histopathological re-review of tumors of the orbit, the conjunctivae and eyelids of patients enrolled on the IRS I, II, III, and IV pilot was performed and clinical data were analyzed to evaluate whether or not a specific morphologic subtype might have a relationship to the clinical behavior of these tumors.

MATERIAL AND METHODS

Two hundred and sixty-four patients with orbital RMS and related sarcomas arising in the orbit, conjunctivae, and eyelids and entered on the IRS I, II, III, and pilot IV were eligible for this study. Adequate histologic material was available for a study re-classification of 229 of these cases. The classifications of the IRS Pathology Committee review were utilized for the remaining 35 cases. All tumor types considered to be eligible for the IRS protocols were included in these analyses (Table I). In addi-

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TABLE I. Histopathologic Classification of Orbital Rhabdomyosarcoma

	Reviewed cases (a)	Non reviewed cases (b)
Embryonal RMS		
Classic	152	25
Botryoid	11	—
Spindle cell	31	—
Anaplastic	2	—
Alveolar RMS	24	—
Undifferentiated sarcoma	4	7
Sarcoma NOS	5	3
TOTAL	229	35

a) Tumors whose histologic material was re-classified for this study.
b) Classification based on the IRS Pathology Committee review performed at the time of patients enrollment on the IRS protocol.
NOS = sarcoma not otherwise specified because of inadequate amount or preservation of available tissue.

tion to rhabdomyosarcoma, small numbers of patients with undifferentiated sarcoma, and sarcomas whose tissues did not permit a precise subclassification because of inadequate amount or poor preservation of tissue (NOS) were included. The classification followed standard diagnostic criteria [9] modified by the recent formulation of two further subsets of embryonal rhabdomyosarcomas, i.e., spindle cell variant [10,11] and anaplastic RMS [12,13]. A lesion was classified as alveolar RMS if *any* alveolar features were present [14,15].

Because early observations suggested that the majority of embryonal RMS of the orbit were less differentiated than usually seen elsewhere in the body, the tumors were subclassified into differentiation categories which has been done in some previous studies [16,17] using conventional hematoxylin and eosin sections. Tumor cell rhabdomyoblastic differentiation was defined by the amount of eosinophilic fibrillary cytoplasm, and differentiation levels by the proportion of cells present. Sarcomas with only occasional isolated rhabdomyoblasts were placed into a poorly differentiated category, D-1. If myoblasts were seen individually scattered or in clusters in most of the medium power fields (objective 20×, eyepiece 10×) the lesion was considered moderately differentiated, D-2. Tumors in which myoblasts predominated throughout the samples were called highly differentiated, D-3.

When histologic material was available, immunohistochemistry (IHC) was utilized to evaluate whether or not rhabdomyogenesis was present. Since the number of slides for the IHC studies was limited, anti-muscle specific antibodies were applied preferentially to other markers. The list of the primary antibodies is shown in Table II. Pepsin (Sigma, St. Louis, MO), 10% in 1N HCl, was used for tissue digestion before use of the primary antibodies (45 min. at 37°C). Immunostaining was performed using the avidin-biotin amplification system (Vectastain ABC reagent). The primary antibodies were substituted by non-immune sera for negative controls. Positive controls were provided with each set of antibodies. All primary antibodies were incubated for 60 minutes and secondary antisera for 30 minutes at room temperature. 3-amino-9-ethylcarbazole (0.2 mg/ml in 0.05 M sodium acetate buffer, pH 5.0), was used as chromogen. The slides were counterstained with Mayer's hematoxylin. The vimentin studies were performed before routine microwave retrieval pretreatment was instituted in our laboratory. A subsequent study of RMS done in our laboratory has shown that all RMS lesions that are reasonably preserved react with anti-vimentin antibodies when the tissue is microwave-treated prior to antibody testing (unpublished observations). Electron microscopy evaluation was not included in this study since material was available in too few patients.

Patients were staged according to the IRS Clinical Grouping Classification. Clinical group I patients had complete removal of localized disease. Clinical Group II patients had gross resection of their tumors with microscopic residual disease, with or without positive regional lymph nodes, or had complete resection of their tumors and resected positive lymph nodes without microscopic disease. Clinical Group III patients had gross evidences of residual tumor following surgery or biopsy, and Clinical Group IV patients had metastatic disease at the time of diagnosis. Curves plotting the distribution of survival time were calculated by the method of Kaplan and Meier [18], and tests of differences among distributions were based on the Gehan-Breslow [19] statistic. Significance levels were based upon two-sided tests. *P* values of 0.05 or less were considered strong statistical evidence against the null hypothesis. Survival time (S) was measured as the time from the start of treatment to death for patients who have died and the time to the latest follow-up for all patients still alive.

RESULTS

Histology and Immunohistochemistry

Results of the re-review of 229 orbital sarcomas as well as the classification of the remaining cases by the IRS Pathology Committee are given in Table I. The analysis of clinical data included all 264 patients. About three-quarters (144 of 196) of the embryonal rhabdomyosarcomas, including botryoid and spindle cell variants, were minimally differentiated (D1, Table III). They consisted of small poorly differentiated cells with small nuclei with homogeneous chromatin pattern, inconspicuous small nucleoli, and poorly developed pale staining cytoplasm sometimes with vacuoles (Fig. 1). Periodic acid Schiff (PAS) reaction often demonstrated small amounts of diastase sensitive glycogen granules. Individual cell death was a common feature. In a third of poorly differ-

TABLE II. Primary Antibodies Used

Antibody	Clonality	Clone	Source	Dilution	Digestion
Actin, anti-muscle specific	M	HHF35	ENZO	1:3000	+
Desmin	P	—	DAKO	1:500	+
Desmin	M	DE-R-11	DAKO	1:25	+
Myoglobin	P	—	DAKO	1:400	+
NSE	M	BBS/NC/VI-H14	DAKO	1:200	−
S-100	P	—	DAKO	1:300	−
S-100	M	15E2E2	BioGenex	1:40	−
Vimentin	M	V9	DAKO	1:25	−

P = polyclonal antibodies, M = monoclonal antibodies
NSE = neuron-specific enolase

TABLE III. Orbital Rhabdomyosarcoma: Degree of Differentiation by Histologic Type

	Differentiation group[a]		
Histologic type	D1	D2	D3
Embryonal, n = 196			
Classical (incl.botryoid)	122	27	14
with anaplasia	1	1	
Spindle cell	21	9	1
Alveolar, n = 24	19	3	2

[a]Described in methods section

entiated rhabdomyosarcomas (D1) myogenesis was found only after a laborious search. Immunohistochemistry demonstrated that these tumors expressed muscle specific antigens. The results are detailed in Table IV. About one third of embryonal RMS also contained cells with large vesicular nuclei and prominent nucleoli. Such nuclei were present both in the immature appearing cells as well as in cells displaying a more advanced myoblastic differentiation (Fig. 2). The number of mitotic figures ranged from 1/10 HPF to 17/10 HPF (objective 40×, eyepiece 10×), depending on cellularity. Two of the 15 embryonal RMS cases with advanced differentiation (D3) consisted of almost entirely mature rhabdomyoblasts, suggesting rhabdomyoma. Both resembled the ''intermediate'' category of fetal rhabdomyoma described recently [20] but there were clusters of undifferentiated cells to classify these tumors as rhabdomyosarcomas (Fig. 3). Two embryonal RMSs had foci of marked anaplasia with large multilobated nuclei.

Thirty-one RMSs had a predominant spindle cell pattern. Twenty-one of these tumors were considered poorly differentiated RMS (Table III); twelve of them had a herringbone and focal cart-wheel pattern resembling the infantile type of fibrosarcoma (Fig. 4a). The spindle cells had PAS positive diastase sensitive granules in their cytoplasm. Rhabdomyoblasts, found only focally and usually in small groups, reacted with muscle-specific actin (4b).

The morphology of the alveolar RMS was typical with alternating pseudoalveolar patterns. Most of the alveolar RMSs were poorly differentiated (Table III). In those cases where the margins of the tumor had been adequately sampled, the tumor was always found to be infiltrative into the adjacent muscle and fat tissues. No instances of so called ''solid'' alveolar RMS were identified in these cases [14]. Two alveolar RMS lesions contained poorly differentiated cells (D1) which were arranged in small clusters forming a highly infiltrative pattern, which were referred to as microalveolar (Fig. 5).

One hundred and ninety of the 432 IRS II non-orbital embryonal RMS cases showed a poorly differentiated pattern, similar to that seen in many of the orbital tumors in this series. The most common non-orbital sites with this morphology were parameningeal sites (nasopharynx, nasal cavity, and sinuses, middle ear), prostate, vagina, and to a lesser extent, urinary bladder. Except for vagina and urinary bladder, all of these sites are considered unfavorable [21,22]. There was a statistically significant difference in survival ($P < 0.001$) between orbital patients with poorly differentiated embryonal RMS and those with similar lesions in extraorbital sites (Fig. 6). The 5-year survival of 144 patients with poorly differentiated embryonal orbital RMS was only slightly better (97 ± 2%) than for those with all types of embryonal tumor combined (94 ± 2%), but significantly better than for those with similar lesions located in other sites (66 ± 3%) (Fig. 7).

Clinical Data

The distribution of patients by clinical group is as follows: Group I, 9 patients (3.4%); Group II, 54 patients (20.4%); Group III, 194 patients (73.5%); Group IV, 7 patients (2.7%). The distribution of patients by study is as follows: IRS I, 74; IRS II, 83; IRS III, 104; IRS IV Pilot, 3.

The average follow-up period for the 253 patients who are alive without disease is 7 years 6 months (range 26 weeks–19 years). Twenty-six patients died; eighteen patients died of progressive disease (7.1%), five of treatment complications (2%) and one of 'other' cause (Table V). Two patients cured of RMS developed a second malignancy and died (one of acute myeloid leukemia as already reported [3] and another of adrenal carcinoma).

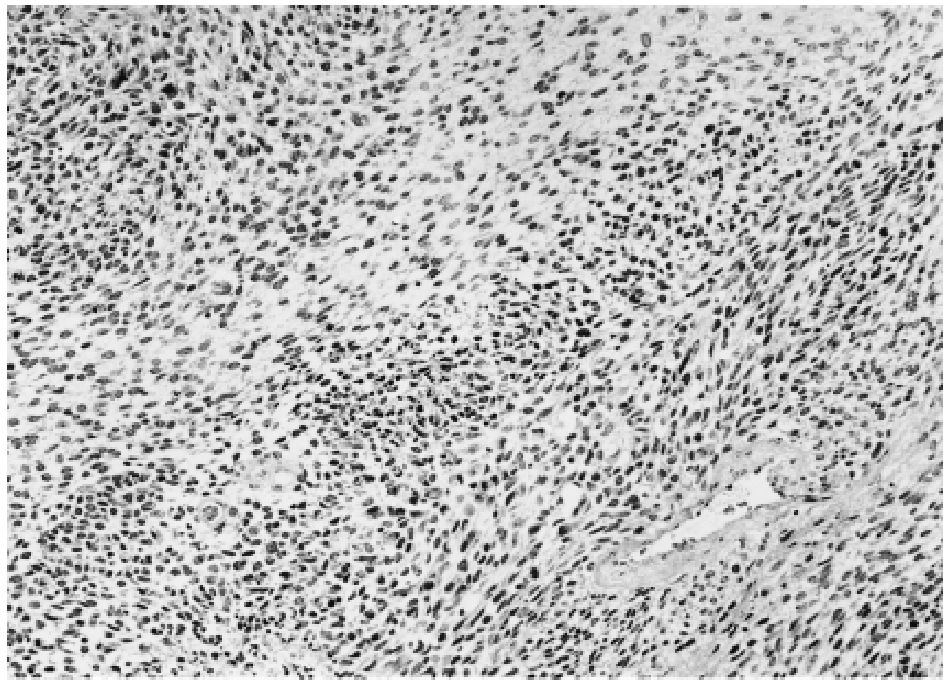

Fig. 1. Poorly differentiated embryonal rhabdomyosarcoma (D1) (original magnification ×25, H&E).

TABLE IV. Immunohistochemistry of Poorly and Moderately Differentiated RMS

Differentiation	Des-p	Des-m	Actin	MG	VIM	S100	NSE
Minimal (D1)	29+/8−	18+/18−	27+/8−	10+/25−	16+/3−	0+/31−	0+/30−
Moderate (D2)	12+/3−	9+/3−	12+/0−	5+/3−	5+/1−	0+/7−	0+/7−

The data show the number of positive and negative cases (+/−). There was a limited number of sections available for some tumors. Immunohistochemistry was not done on highly differentiated RMS (D3).
Des-P = Polyclonal desmin; Des-m = Monoclonal desmin; Actin + muscle specific actin; MG = Myoglobin; VIM = vimentin; NSE = neurone specific enolase.

One of 63 clinical group I and II patients died of disease. The remaining 17 patients with disease had incomplete excision of their tumor or metastatic disease at diagnosis. The average survival interval for all patients who died with disease was 136 weeks (range 2–268 weeks). Two clinical group IV patients are alive without evidence of the disease 5 years and 12 years after the start of treatment. Only six (2.7%) of the 219 patients with embryonal RMS died; one patient had a tumor with marked anaplasia. None of the patients with spindle cell, highly differentiated RMS, or botryoid morphology died of disease. One of 11 patients with undifferentiated sarcoma died.

In contrast, eight of 18 patients (44%) who died of progressive disease had alveolar RMS. The tumors of the remaining four patients were classified as undifferentiated sarcoma in one and sarcoma NOS in three. There was statistically significant evidence of differing survival ($P < .001$) among patients with embryonal RMS, alveolar RMS, and undifferentiated sarcoma. The estimated 5-year survival by group was 94 ± 2% for embryonal, 74 ± 9% for alveolar and 91 ± 9% for undifferentiated sarcoma.

There was no obvious sex predilection for this tumor (F:M ratio 1:0.89). Two hundred and twenty-six patients were Caucasians, 26 Afro-Americans, 3 orientals, 8 ''other,'' and one unknown. The average age at diagnosis was 6 years 1 month, with median being 5 years. Thirteen patients developed the tumor in the first year of life, the youngest being a one month old boy. Of these, only six are alive and well. All five patients with alveolar RMS and one of four with undifferentiated sarcoma died of disease. One of four with embryonal RMS died of complications of treatment.

DISCUSSION

Orbital rhabdomyosarcoma account for 9% of all RMS [23,24]. Of all patients with RMS treated with multimodal therapy, those with primary lesions at this site have the most favorable outcome in spite of the fact that three-fourths have residual tumor after initial surgery.

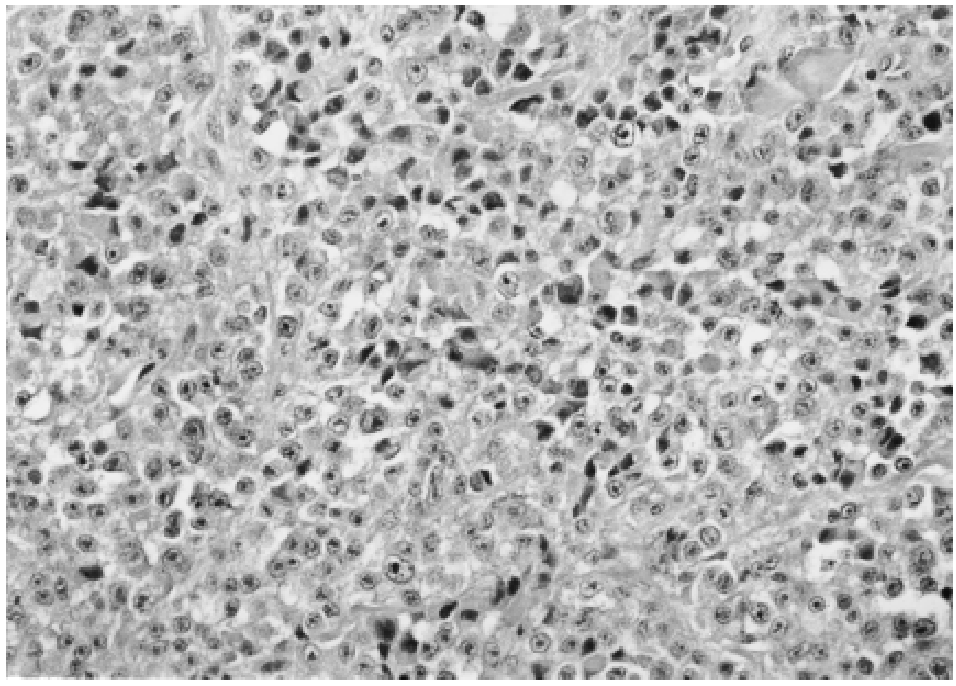

Fig. 2. Moderately differentiated embryonal rhabdomyosarcoma (D2) (original magnification ×50, H&E).

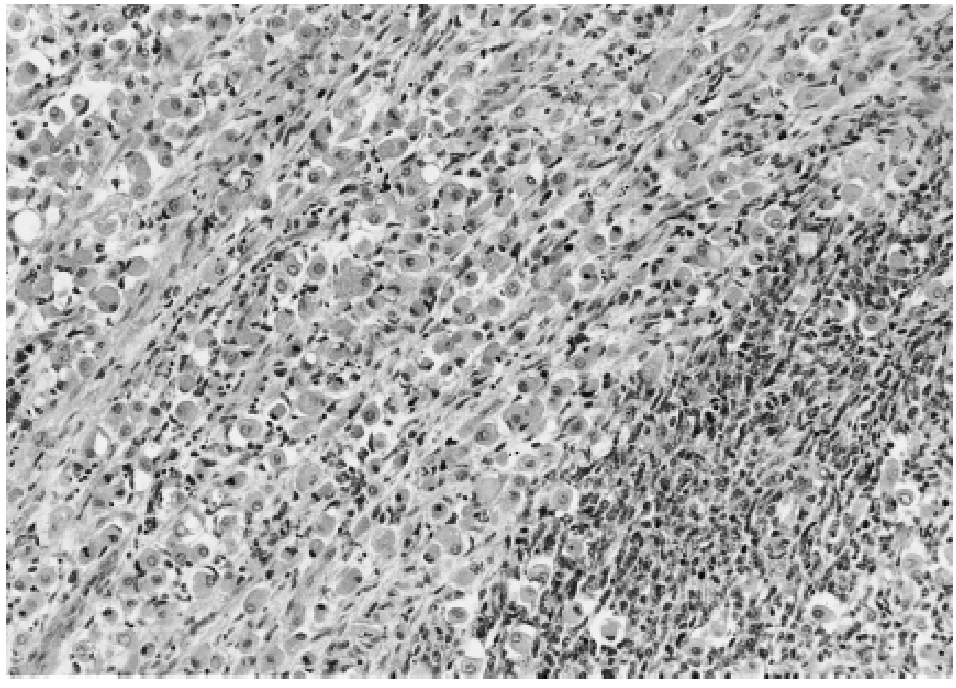

Fig. 3. Highly differentiated embryonal rhabdomyosarcoma (original magnification ×25, H&E).

Recent reports of orbital RMS have focused on clinical presentation and results of therapy [2,4,6]. This study was undertaken to evaluate the possibility that tumor morphology may have influenced the superior survival rate. Histopathological examination of all orbital sarcomas from patients entered on the IRS showed that embryonal RMS predominated, accounting for 83% of all such lesions compared with 54% for all sites combined in the 1628 patients that were eligible for IRS I and II [22] which is comparable to other previously reported studies [5,6,25]. A small fraction of patients had a botryoid subtype involving the conjunctiva and adjacent soft tissues (5.6% of all reviewed embryonal RMS). Nine percent of the 264 patients had alveolar RMS, significantly lower

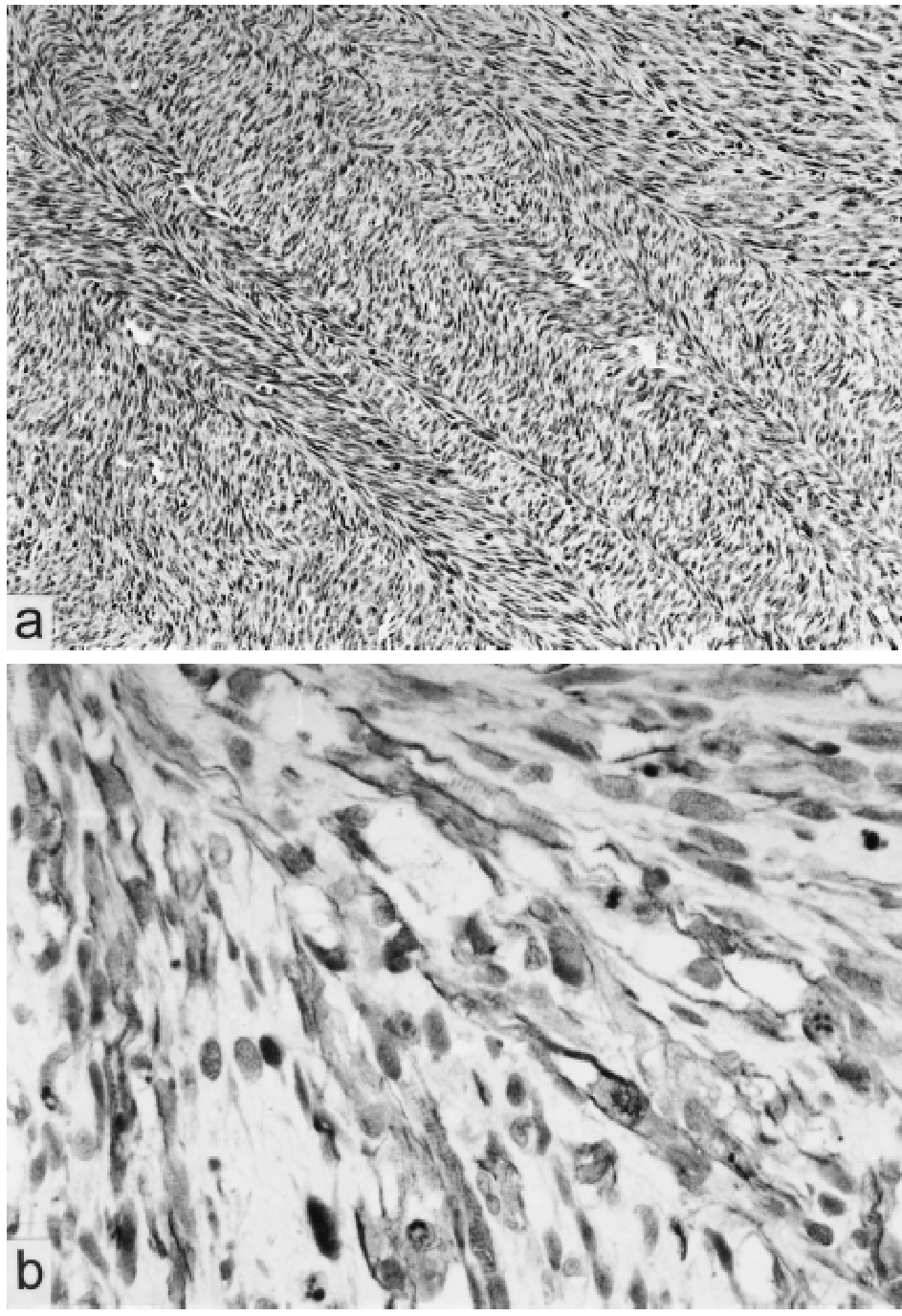

Fig. 4. (a) Cellular spindle cell foci of embryonal rhabdomyosarcoma resembling to the infantile type of fibrosarcoma, (original magnification ×25) (H&E); (b) spindle cell rhabdomyosarcoma showing rhabdomyoblastic differentiation with immunoreaction to anti-muscle specific actin antibody (original magnification ×100).

than the 21% incidence of alveolar RMS in 1628 IRS I and II patients [23]. The majority of orbital embryonal RMSs were poorly differentiated but not as immature as tumors classified as embryonal sarcoma by others [23].

The role of morphology in influencing the excellent prognosis is still a subject of controversy. A multivariate analysis done on IRS II patients showed that the most important determinants of prognosis are the site of the primary tumor, extent of disease at diagnosis, and tumor size [7,21,26]. A working concept for this study was that the predominant poorly differentiated RMS seen in the orbit may be more sensitive to treatment. Only two studies have previously evaluated the relationship of pretreatment embryonal RMS cell maturity to tumor response and patient survival. The International Society for Pediatric Oncology investigators showed that patients

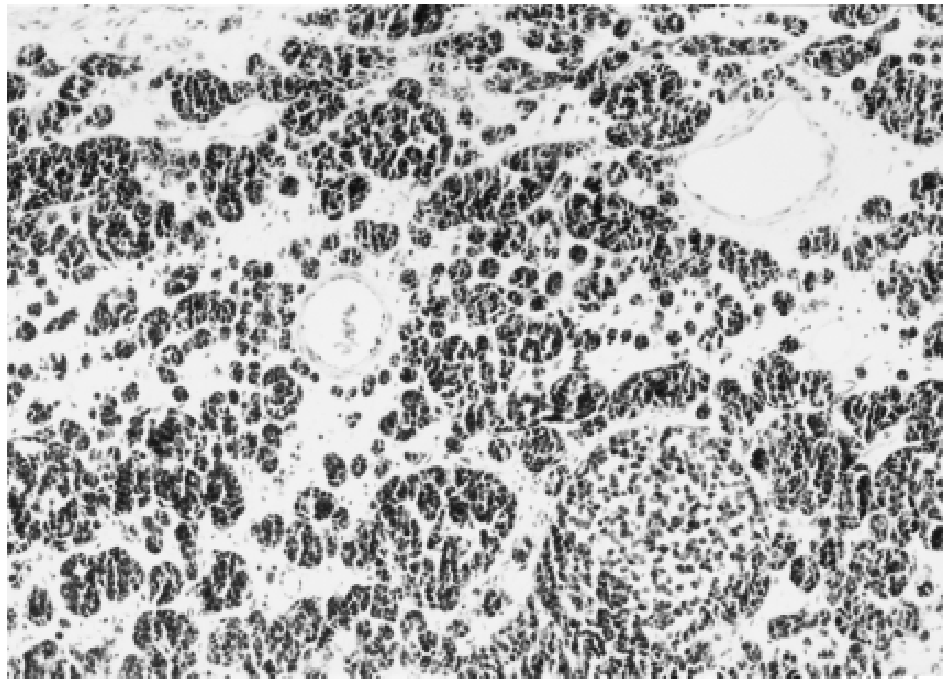

Fig. 5. Primitive poorly differentiated alveolar rhabdomyosarcoma with small clusters of tumor cells-''microalveolar'' (original magnification ×25).

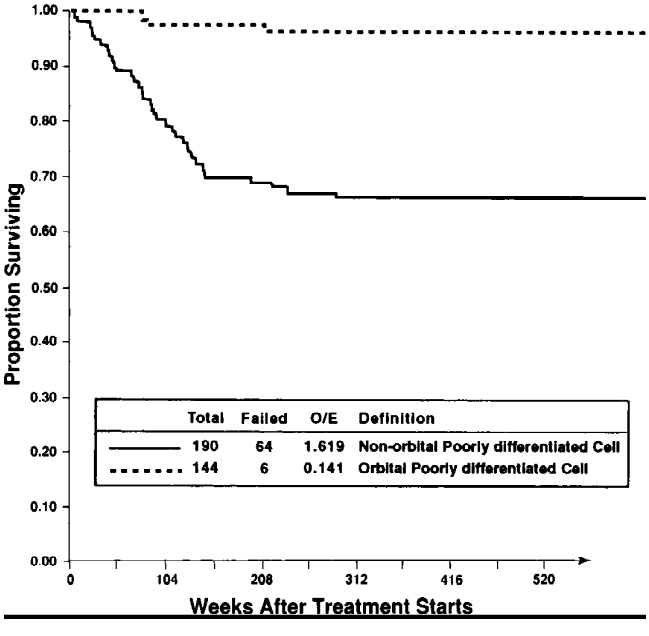

Fig. 6. Kaplan-Meier survival estimates comparing poorly differentiated type of embryonal rhabdomyosarcomas of the orbit and similar rhabdomyosarcomas occurring elsewhere in the body.

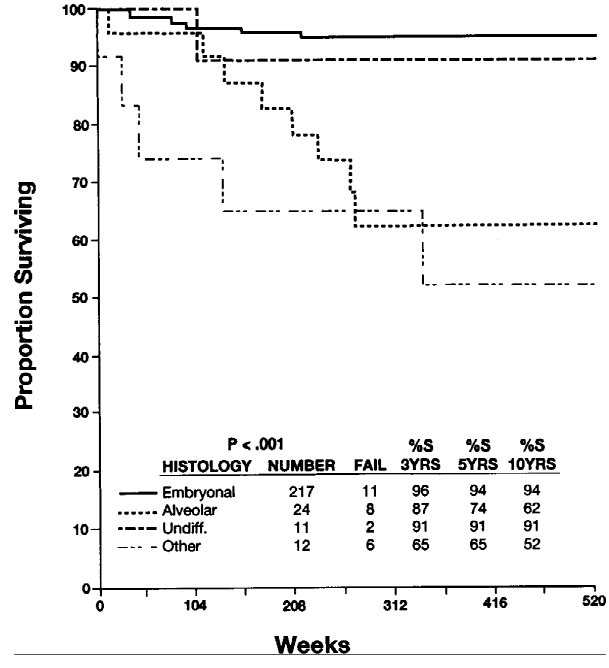

Fig. 7. Kaplan-Meier survival estimates comparing embryonal RMS, alveolar RMS, undifferentiated sarcomas, and other sarcomas of 264 orbital patients treated on IRS I, II, III, & pilot IV protocols.

with poorly differentiated embryonal RMS classified as loose non-botryoid and dense poorly differentiated embryonal RMS had a poorer outcome than those with well-differentiated embryonal RMS and botryoid variants [23]. The German Cooperative Soft Tissue Tumor Study classified sixty-four embryonal RMSs, dividing them into poorly, intermediate, and well differentiated tumors. The tumor responses were clearly better in the more differentiated lesions [16].

Recent studies have identified a spindle cell subset of embryonal RMS with a more favorable behavior [10,11].

TABLE V. Clinicopathologic Data on Patients With Orbital RMS Who Died

Age/ sex	IRS group	Histology/ differentiation	Cause of death	Survival (weeks)
<1/f	III	Undifferentiated	Progression	407
<1/F	III	Alveolar/D1	Progression	263
<1/M	IV	Alveolar/D1	Progression	11
<1/F	III	Alveolar/D1	Progression	111
<1/F	III	Alveolar/D1	Progression	268
<1/F	IV	Alveolar/D2	Progression	204
<1/F	IIA	Embryonal/na	Infection	33
1/F	IV	NOS	Progression	43
1/F	IV	NOS	Progression	25
1/M	III	Alveolar/D1	Progression	133
1/M	III	Embryonal/D1	Progression	230
1/F	III	Embryonal/D1	Progression	93
2/F	III	NOS	Progression	2
2/M	III	Alveolar/D1	Progression	231
4/M	IV	Alveolar/D1	Progression	173
5/F	III	Embryonal/D1	Infection	3
6/F	III	Embryonal/D2	Progression	212
7/M	IIA	Undifferentiated	Adrenal CA	486+
8/M	III	Embryonal/D1	Infection	78
8/F	III	Embryonal/D1	Infection	1
9/M	IIA	Embryonal/D1	Progression	61
10/F	III	Embryonal/D1	Progression	82
11/F	III	NOS	Other	339
13/M	III	NOS	AML	131
14/F	III	Embryonal/D1	Infection	150
15/M	III	Embryonal/D2	Progression	115

na = slides not available for the current reclassification.

This type occurs most often in the paratesticular region and is associated with a very favorable outcome, whereas in other sites the behavior is not significantly better than that of other embryonal RMS subtypes [11]. This type of RMS is relatively well differentiated. The tumors either show marked collagen production or a more cellular appearance resembling a leiomyosarcoma [10,11,28]. We observed 31 embryonal RMS of the spindle cell type in the orbit. Twelve of these resembled infantile fibrosarcoma [9,29,30], but minimal rhabdomyoblastic differentiation was found in all. A similar variant of RMS with a less prominent herringbone-like pattern capable of metastasizing was recently described as infantile rhabdomyofibrosarcoma [30]. The differential diagnosis of spindle cell RMS includes malignant Triton tumor [31] but the immunostaining for S-100 protein of our tumors was uniformly negative. Moreover, the spindle cells had demonstrable glycogen in their cytoplasm, not usually present in neural tumors, fibrosarcomas, and fibrous histiocytomas. None of the study patients is known to have von Recklinghausen's disease, but these data were not systematically collected in these cases. All patients with spindle cell RMS in the orbit are alive and well suggesting that the tumor morphology may have been a factor influencing the favorable outcome.

A surprising finding in this study was the 5-year survival of 10 of 11 of the patients with undifferentiated sarcoma. One hundred and thirty-five patients with this diagnosis in IRS I and II had a 53% three-year survival rate [22].

In striking contrast, there was a statistically significant difference between the survival of patients with primary orbital sarcoma of the alveolar subtype compared to the embryonal subtype ($p < .001$). This supports previous reports that alveolar rhabdomyosarcoma portends an unfavorable prognosis [8,22,31–34], now including patients with an orbital primary site. In IRS I and II [22,33] alveolar morphology was associated with unfavorable survival rates in patients with clinical group I and II disease. When treated more aggressively, IRS III patients with the alveolar RMS subtype fared like those with embryonal RMS [35].

Immunohistochemistry is helpful in differentiating poorly differentiated RMS from other poorly differentiated sarcomas [36–42]. Immunohistochemistry performed on a subset of orbital RMS tumors with minimal differentiation demonstrated that 78% were positive with anti-desmin (polyclonal) and 77% positive with anti-actin antibodies. Surprisingly, 29% of poorly differentiated embryonal RMS showed scattered cells positive to anti-myoglobin antibodies. Myoglobin is generally thought to be a specific marker of striated muscle cells [17,37,43], present in differentiated rhabdomyoblasts, and only rarely reported in histologically poorly differentiated rhabdomyoblasts [44]. The results with anti-myoglobin antibodies in this study may be due to tissue digestion by pepsin or, more likely, due to the use of a more sensitive avidin-biotin detection system than the PAP method utilized in some of the earlier studies. The negative reaction to vimentin in 4 cases of RMS is considered to be due to the fact that these tissues were not pre-heated by microwave.

While an age of less than a year at diagnosis was not proven to be a significant prognostic factor in a previous IRS study [45], the age of children with orbital RMS deserves special consideration. Six of 13 infants under one year of age died of disease progression. Five of them had alveolar RMS and one had undifferentiated sarcoma which is similar to the report of Salloum et al. [46]. Another study showed that patients with alveolar RMS under 5 years of age fared worse than those between 5 and 10 years [47]. The reason for a more aggressive behavior of orbital alveolar RMS in infants is not certain. An important factor may be the reduced intensity of therapy which infants receive [46]. However, the prevalence of alveolar morphology among patients who died with tumor progression gives further evidence that this type is a significant predictor of unfavorable outcome, particularly in infants.

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